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(57) Abstract

This invention provides a nutritional product and method for delivering glutamine to a patient. The nutritional product has a protein source which includes a cereal protein. The cereal protein may be oat protein, sorghum protein, or millet protein. The nutritional product also includes a carbohydrate source and a lipid source.

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Product and Method for Providing Glutamine

This invention relates generally to the treatment and nutritional support of patients. More specifically, this invention relates to nutritional products and treatments designed to provide supplemental glutamine to persons in need thereof.

The amino acid glutamine has many important functions in the body. For example, glutamine acts as the primary vehicle for transfer of amino nitrogen from skeletal muscle to visceral organs, as a fuel for the rapidly dividing cells of the gastrointestinal tract and immune system, and as a substrate that permits the kidneys to excrete acid loads and protect the body against acidosis. Further, there is increasing evidence that glutamine is essential to the proper functioning of host defence mechanisms and wound healing.

Despite these functions, glutamine is traditionally classified as non-essential amino acid. The reason is that the body is generally able to synthesise sufficient glutamine for its needs from glutamate and glutamic acid. Also, glutamine is the most abundant amino acid in the blood and free amino acid pool of the body. However, this is only true in periods of good health and does not apply to pre-term babies. During periods of illness, the metabolic rate of glutamine increases and the body is not able to synthesise sufficient glutamine to meet its needs. This is particularly true during episodes of stress such as sepsis, injury, burns, inflammation, diarrhoea and surgery. During episodes of stress, there is a marked increase in glutamine consumption by the gastrointestinal tract, immune cells, inflammatory tissue and the kidney. This consumption may far outstrip the endogenous rate of synthesis of glutamine. As the deficiency becomes manifest, tissue function alters, morphological changes may be observed, and a negative nitrogen balance arises. Similarly, pre-term babies have a lower rate of glutamine synthesis; often insufficient for needs. Further, it is found that athletes, after intense exercise, have reduced levels of glutamine in their plasma.

The administration of glutamine supplemented diets to patients during periods of stress has resulted in improvement of the person's condition. For example, glutamine supplemented diets have been shown to regenerate muco-proteins and intestinal epithelium, support gut barrier function, shorten hospital stay, improve immune function, and enhance patient survival (Stehle *et al*; 1989; *Lancet*, **1**:231-3; Hammerqvist *et al*; 1989; *Ann. Surg.*; **209**:455-461; Li *et al*; 1995; *J. Parenter. Enteral Nutr.*, **18**, 303-307 and Gianotti *et al*; 1995; *J.*

Parenter. Enteral Nutr., **19**, 69-74). Therefore glutamine is now considered to be a conditionally essential amino acid for critically ill and other stressed patients (Lacey *et al*; 1990; *Nutrition Review*, **48**:297-309).

The additional need for glutamine during periods of stress must come from an exogenous source such as diet. However the supplementation of nutritional formulas with glutamine has traditionally not been performed because glutamine has long been considered to be a non-essential amino acid. Also glutamine is only slightly soluble in water and, more importantly, is relatively unstable in solution. To overcome the stability problem, it has been proposed to supplement powdered formulas with L-glutamine. These formulas are then reconstituted immediately prior to administration. However, for enteral formulas, this approach has not proved to be particularly successful since glutamine in its free form may be converted to glutamate by stomach acids prior to absorption. Also, health care professionals prefer ready-to-consume liquid formulas as opposed to powdered formulas.

Another method of supplementing diet with glutamine has centred on the use of gluten or gluten hydrolysates as a protein source for nutritional compositions. Gluten is particularly rich in glutamine and is hence a good source of glutamine. Also, the use of gluten or a gluten hydrolysate offers the advantage of providing the glutamine in a form which is stable and relatively soluble. However gluten is potentially allergenic and this has severely limited its use in nutritional formulas. This problem may be ameliorated to some extent by using a gluten hydrolysate instead of gluten and a nutritional composition based on gluten hydrolysate is commercially available under the trade name Nutricomp® Immun. However, although the risk from allergenic reaction is much reduced, it has not been removed entirely.

A yet further approach has been to supplement nutritional formulas with synthetic dipeptides such as L-alanyl-L-glutamine or L-glycyl-L-glutamine. These dipeptides are stable in solution and have been shown to be an effective form of glutamine supplementation. However, synthetic peptides of this nature may significantly increase the cost of the nutritional formulas.

Therefore, there is a need for a nutritional product or method for delivering glutamine to patients.

This invention provides a nutritional product for delivering supplemental glutamine to a person or animal in need thereof.

Accordingly, in one aspect, this invention provides an enterally administrable, nutritional product for delivering glutamine to a person in need thereof, the product comprising a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof.

It has been surprisingly discovered that certain cereal proteins provide an excellent source of glutamine in a form which is stable and readily absorbed. Also, these cereal protein provide very little or no risk of inducing allergenic reactions since they contain little or no gluten. Further, the protein source has a good amino acid profile and excellent overall nutritional value. Another advantage is that the nutritional product contains a protein source which is less expensive than casein and whey.

Preferably, the protein source includes about 30% to about 95% by weight of at least one of the cereal proteins; for example about 50% to about 90% by weight. More preferably, the remaining about 70% to about 5% by weight of the protein source comprises casein, whey, or free amino acids, or a mixture thereof. It is especially preferred for the protein source to include a source of lysine; for example in the form of free amino acids.

Preferably the protein source comprises from about 15% to about 35% of the total calories of the nutritional product.

The nutritional product may include a carbohydrate source. The carbohydrate source may comprise about 35% to about 60% of the total calories of the nutritional product.

The nutritional product may also include a lipid source. The lipid source preferably comprises about 20% to about 40% of the total calories of the nutritional product.

In an embodiment, the nutritional product is provided in a liquid form for enteral feeding. Preferably the nutrition product is in ready-to-drink liquid form.

In another aspect, this invention provides a nutritional product for delivering glutamine to a person in need thereof, the product comprising a protein source which includes a cereal protein selected from oat bran protein, sorghum protein and millet protein, or mixtures thereof; and a source of lysine.

In yet another aspect, this invention provides a method for delivering glutamine to a person or animal. The method includes a step of administering to a the person or animal a therapeutically effective amount of a nutritional product

comprising a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof.

Preferably the nutritional product is enterally administered to the patient.

In yet another aspect, this invention provides a method of increasing plasma glutamine levels in a human or animal, the method comprising enterally administering to the human or animal an effective amount of a nutritional composition having a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof.

Preferably the human or animal is a stressed patient, a pre-term baby, or an athlete. Examples of stressed patients are patients who are critically ill, or who are suffering from sepsis, injury, burns, or inflammation, or patients recovering from surgery.

In a further aspect, this invention provides a method of improving the immune function of a stressed patient or athlete by providing glutamine to the patient, the method comprising administering to the patient or athlete an effective amount of a nutritional composition having a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof.

In a further aspect, this invention provides a method of providing glutamine to patients suffering from injured or diseased intestines or to maintain the physiological functions of the intestine, the method comprising enterally administering to the patient an effective amount of a nutritional composition having a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof.

In a yet further aspect, this invention provides the use of a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof, in the preparation of an enterally administrable, nutritional composition for providing glutamine to a human or animal.

Additional features and advantages of the invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

This invention relates to the provision of glutamine to humans and animals. Glutamine is an important nutrient because it promotes regeneration of mucoproteins and the intestinal epithelium. Hence, glutamine is an important supplement for patients suffering from intestinal injury or disease, immune disorders, or any of a wide variety of diseases affecting the connective and

supporting tissues. However, the use of free glutamine or synthetic glutamine containing peptides is not feasible due to the high cost and low stability of these compounds.

However, it has now been found that cereal proteins selected from oat protein, sorghum protein and millet protein, are rich in glutamine and, when properly prepared, can serve as both a protein source and glutamine source in a nutritional product.

Many attempts at determining the glutamine content of proteins have been made in the past. All reported attempts have used techniques based upon acid hydrolysis of the protein followed by automated amino acid analysis. Although these techniques provide reasonably accurate results for most amino acids, they provide very poor results for glutamine. The reason is that glutamine breaks down in the presence of heat and acid to form glutamic acid and ammonia. Consequently almost all of the reported analyses of proteins report glutamine and glutamic acid as a summation value; if reported at all. However procedures have recently been developed which permit the accurate determination of protein and peptide bound glutamine. For example, methods involving the conversion of glutamine residues to acid stable L-2,4-diaminobutyric acid in the presence of bis(1,1-trifluoroacetoxy)iodobenzene (Kuhn *et al*; 1996; *J. Parent. Enteral Nutr.*, **20**, 4:292-295) or methods involving the enzymatic hydrolysis of the protein. When analysed using these techniques, certain cereal proteins have now been found to contain relatively high contents of glutamine. For example, oat protein has a glutamine content of about 16 to about 20 g/100 g amino acids; sorghum protein has a glutamine content of about 16 g/100 g amino acids; and millet protein has a glutamine content of about 19 g/100 g amino acids. Further these proteins contain very little gluten and hence have a low risk of inducing gluten-related, allergenic reactions. In other words, these proteins provide an excellent source of dietary glutamine.

The protein may be added in whole or hydrolysed form. Further, peptide mixtures may also be fractionated by chromatographic methods to produce glutamine rich peptide segments which can be added to enteral diets and clinical foods. Also, selected fractions of the cereal proteins are even richer in glutamine than the proteins themselves and provide an excellent source of glutamine. For example, oat bran concentrates are very rich in glutamine.

The protein source preferably provides approximately 15% to 30% of the total calories of the nutritional product. Further, preferably approximately 50% to

90% by weight of the protein source is selected from oat protein, sorghum protein and millet protein, or mixtures thereof. The remaining approximately 50% to 10% of the protein source may be another suitable protein, such as casein, whey, soy or mixtures thereof, or may comprise free amino acids or salts thereof. Preferably the remaining protein source is enriched in lysine; either in the form of lysine-rich proteins or peptides or as a free amino acid. Preferably lysine in the form of a free amino acid, or salt thereof, provides up to about 4% by weight of the protein source.

The protein source preferably has well balanced amino acid profile which fulfils the recommendations of the FAO/WHO expert committee for the essential amino acid requirements for children > 2 years of age.

In a preferred embodiment, protein source provides approximately 25% of the caloric content of the nutritional product. The cereal protein preferably comprises approximately 85% to 90% by weight of the protein source. In a preferred embodiment, whey or casein comprises about 5% to about 10% by weight of the protein source.

The carbohydrate source preferably provides approximately 35% to 60% of the total calories of the nutritional product. In a preferred embodiment, carbohydrate source provides approximately 45% of the caloric content. Several carbohydrates may be used including maltodextrin, corn starch, corn syrup solids or sucrose, and mixtures thereof. In a preferred embodiment, corn syrup solids comprise approximately 62% of the carbohydrate source and sucrose comprises approximately 38% of the carbohydrate source. Preferably the carbohydrate source is lactose free.

The lipid source may provide approximately 20% to 40% of the total caloric content of the nutritional composition. In a preferred embodiment, the lipid content comprises approximately 30% of the total caloric content of the nutritional composition. The lipid source may include a mixture of medium chain triglycerides (MCT) and long chain triglycerides (LCT). For example, the lipid source may include at about 20% to about 80% by weight of medium chain triglycerides. For example, medium chain triglycerides may make up about 70% by weight of the lipid source. Suitable sources of long chain triglycerides are canola oil, olive oil, soy oil, milk fat, corn oil, residual milk fat, and soy lecithin, or mixtures thereof. Coconut oil is a suitable source of medium chain triglycerides.

Preferably, the lipid source has an ω-6:ω-3 ratio ranging from about 4:1 to about 15:1. For example, the ω-6 to ω-3 ratio is approximately 5:1. The ratio of

calories to grams of nitrogen (CAL/gN) is preferably approximately 91:1. The NPC/gN ratio is approximately 68:1.

In a preferred embodiment, the lipid source is provided by a combination of corn oil (14% by weight), canola oil (30% by weight), coconut oil (50% by weight), soy lecithin (6% by weight) and residual milk fat (less than 1% by weight).

The nutritional product preferably includes a specialised vitamin and mineral profile. The product may include a source of vitamins and minerals including approximately 75% to about 250% of the recommended daily allowance per 1000 Kcal of the product administered.

The nutritional product may be administered either enterally or parenterally. Suitable enterally administered forms are soluble powders, liquid concentrates, or ready-to use liquid formulations. In a preferred embodiment, the nutritional product is a ready-to-use liquid formulation. Such a formulation may be tube-fed to a patient or fed by having the patient drink the formulation. Preferably, the caloric density of the formulation is approximately 1.0 Kcal per ml. Various flavours, fibres and other additives may also be present. The nutritional product may also be in the form of common foodstuffs; for example yoghurts, soups, pastas, porridges, breakfast cereals, convenience foods such as muesli bars, and the like. For animals such as pets, the composition may be in the form of dried or canned pet food.

The nutritional product may be produced as is conventional; for example, for formulas, the nutritional product may be prepared by blending together the protein source, the carbohydrate source, and the lipid source. If used, the emulsifiers may be included in the blend. The vitamins and minerals may be added at this point but are usually added later to avoid thermal degradation. Any lipophilic vitamins, emulsifiers and the like may be dissolved into the lipid source prior to blending. Water, preferably water which has been subjected to reverse osmosis, may then be mixed in to form a liquid mixture. The temperature of the water is conveniently about 50°C to about 80°C to aid dispersal of the ingredients. Commercially available liquefiers may be used to form the liquid mixture.

The liquid mixture may then be thermally treated to reduce bacterial loads. For example, the liquid mixture may be rapidly heated to a temperature in the range of about 80°C to about 110°C for about 5 seconds to about 5 minutes. This

may be carried out by steam injection or by heat exchanger; for example a plate heat exchanger.

The liquid mixture may then be cooled to about 60°C to about 85°C; for example by flash cooling. The liquid mixture is then homogenised; for example in two stages at about 7 MPa to about 40 MPa in the first stage and about 2 MPa to about 14 MPa in the second stage. The homogenised mixture may then be further cooled to add any heat sensitive components; such as vitamins and minerals. The pH and solids content of the homogenised mixture is conveniently standardised at this point.

If it is desired to produce a powdered nutritional product, the homogenised mixture is transferred to a suitable drying apparatus such as a spray drier or freeze drier and converted to powder. The powder should have a moisture content of less than about 5% by weight. If it is desired to produce a liquid nutritional product, the homogenised mixture is preferably aseptically filled into suitable containers. Aseptic filling of the containers may be carried out by pre-heating the homogenised mixture (for example to about 75 to 85°C) and then injecting steam into the homogenised mixture to raise the temperature to about 140 to 160°C; for example at about 150°C. The homogenised mixture may then be cooled, for example by flash cooling, to a temperature of about 75 to 85°C. The homogenised mixture may then be homogenised, further cooled to about room temperature and filled into containers. Suitable apparatus for carrying out aseptic filling of this nature is commercially available.

The nutritional product may be used as a nutritional support. In particular, the nutritional product may be used to provide nutrition and glutamine to animals and humans. In particular, the nutrition product may be used to provide nutrition and glutamine to stressed patients; for example for patients who are critically ill, or who are suffering from sepsis, injury, burns, or inflammation, or patients recovering from surgery. Further, the nutritional product may be used to provide glutamine to patients suffering from injured or diseased intestines or to maintain the physiological functions of the intestine. Moreover, the nutritional product may be used to raise plasma glutamine levels in humans and animals.

The nutritional product may also be used to provide glutamine to athletes after intense exercise or to pre-term babies.

It is to be understood that, although the nutritional product is intended primarily for patients who require supplemental glutamine, it may also be used as a source of nutrition for people who are not suffering from any illness or condition.

The nutritional product may form the sole source of nutrition or form a supplement to other nutritional sources; including parenterally administered nutrition.

The amount of the nutritional product required to be fed to an ill patient will vary depending upon factors such as the patient's condition, the patient's body weight, the age of the patient, and whether the nutritional product is the sole source of nutrition. However the required amount may be readily set by a medical practitioner. In general, sufficient of the nutritional product is administered to provide the patient with about 1 g protein to about 4.0 g protein per kg of body weight per day. For example, an adult, critically ill patient may be administered about 1.5 g protein to about 2.0 g protein per kg of body weight per day, a pre-term infant may be administered about 2.0 g protein to about 4.0 g protein per kg of body weight per day, and a infant may be administered about 2.0 g protein to about 3.0 g protein per kg of body weight per day. Further, for stressed patients, sufficient of the nutritional product is preferably administered to provide the patient with about 10g to about 25 g of glutamine per day. The nutritional product may be taken in multiple doses, for example 2 to 5 times, to make up the required daily amount or may taken in a single dose.

The nutritional product also provides a source of glutamic acid.

Of course, it will be appreciated that a variety of formulations are possible in accordance with this invention. By way of example, and not by limitation, an example of a suitable nutritional product is as follows:

Example 1

A suitable product that may be utilised as an enteral diet or a liquid diet taken orally is as follows:

Caloric Density	1.0 kcal/ml
Protein	25% kcal (62.5 g/l)
Casein:Oat Protein:Lysine (10:88:2)	
Carbohydrate	45% kcal (112.7 g/l)
Corn Syrup Solids	62% kcal
Sucrose	38% kcal
Lipid	30% kcal (34.6 g/l)
Corn Oil	14% by weight
Canola Oil	30% by weight
MCT (Coconut Oil)	50% by weight
Soy Lecithin	6% by weight
Residual Milk Fat	<1% by weight
ω6:ω3 Ratio	5:1
CAL/gN Ratio	91:1
NPC/gN Ratio	68:1
Vitamins	**Per Litre**
Vitamin A (IU)	4000
b-Carotene (mg)	2.0
Vitamin D (IU)	400
Vitamin E (IU)	60
Thiamin (mg)	3.0
Pyridoxine (mg)	4.0
Biotin (μg)	400
Minerals	**Per Litre**
Zinc (mg)	24
Copper (mg)	2.0
Magnesium (mg)	4.0
Selenium (μg)	100
Sodium (mg)	876
Potassium (mg)	1500
Chloride (mg)	1300

Example 2

Another suitable product is as follows:

Caloric Density	1.0 kcal/ml
Protein	25% kcal (62.5 g/l)
Oat Protein:Sweet whey:Lysine (90:8:2)	
Carbohydrate	45% kcal (112.7 g/l)
Corn Syrup Solids	62% kcal
Sucrose	38% kcal
Lipid	30% kcal (34.6 g/l)
Corn Oil	14% by weight
Canola Oil	30% by weight
MCT (Coconut Oil)	50% by weight
Soy Lecithin	6% by weight
Residual Milk Fat	<1% by weight
ω6:ω3 Ratio	5:1
CAL/gN Ratio	91:1
NPC/gN Ratio	68:1
Vitamins	**Per Litre**
Vitamin A (IU)	4000
b-Carotene (mg)	2.0
Vitamin D (IU)	400
Vitamin E (IU)	60
Thiamin (mg)	3.0
Pyridoxine (mg)	4.0
Biotin (μg)	400
Minerals	**Per Litre**
Zinc (mg)	24
Copper (mg)	2.0
Magnesium (mg)	4.0
Selenium (μg)	100
Sodium (mg)	876
Potassium (mg)	1500
Chloride (mg)	1300

Example 3

Another suitable product is as follows:

Caloric Density	1.0 kcal/ml
Protein	25% kcal (62.5 g/l)
Millet:Sweet Whey:Lysine (82:15:3)	
Carbohydrate	45% kcal (112.7 g/l)
Corn Syrup Solids	62% kcal
Sucrose	38% kcal
Lipid	30% kcal (34.6 g/l)
Corn Oil	14% by weight
Canola Oil	30% by weight
MCT (Coconut Oil)	50% by weight
Soy Lecithin	6% by weight
Residual Milk Fat	<1% by weight
ω6:ω3 Ratio	5:1
CAL/gN Ratio	91:1
NPC/gN Ratio	68:1
Vitamins	Per Litre
Vitamin A (IU)	4000
b-Carotene (mg)	2.0
Vitamin D (IU)	400
Vitamin E (IU)	60
Thiamin (mg)	3.0
Pyridoxine (mg)	4.0
Biotin (μg)	400
Minerals	Per Litre
Zinc (mg)	24
Copper (mg)	2.0
Magnesium (mg)	4.0
Selenium (μg)	100
Sodium (mg)	876
Potassium (mg)	1500
Chloride (mg)	1300

Example 4

Another suitable product is as follows:

Caloric Density	1.0 kcal/ml
Protein	25% kcal (62.5 g/l)
Sorghum:Sweet Whey:Casein:Lysine (85:7:5:3)	
Carbohydrate	45% kcal (112.7 g/l)
Corn Syrup Solids	62% kcal
Sucrose	38% kcal
Lipid	30% kcal (34.6 g/l)
Corn Oil	14% by weight
Canola Oil	30% by weight
MCT (Coconut Oil)	50% by weight
Soy Lecithin	6% by weight
Residual Milk Fat	<1% by weight
ω6:ω3 Ratio	5:1
CAL/gN Ratio	91:1
NPC/gN Ratio	68:1
Vitamins	Per Litre
Vitamin A (IU)	4000
b-Carotene (mg)	2.0
Vitamin D (IU)	400
Vitamin E (IU)	60
Thiamin (mg)	3.0
Pyridoxine (mg)	4.0
Biotin (μg)	400
Minerals	Per Litre
Zinc (mg)	24
Copper (mg)	2.0
Magnesium (mg)	4.0
Selenium (μg)	100
Sodium (mg)	876
Potassium (mg)	1500
Chloride (mg)	1300

All of the products of examples 1 to 4 have an amino acid profile which fulfils the recommendations of the FAO/WHO expert committee for the essential amino acid requirements for children > 2 years of age.

It should be understood that various changes and modifications to the embodiments described will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Claims:

1. An enterally administrable, nutritional product for delivering glutamine to a person in need thereof, the product comprising a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof, the protein source providing about 15% to about 35% of the total energy of the product.

2. A product according to claim 1 which is in the form of a powder, a liquid concentrate, or a liquid ready for enteral feeding.

3. A product according to claim 1 in which the cereal protein comprises about 30% to about 95% by weight of the protein source.

4. A product according to claim 3 in which the protein source further comprises a source of lysine.

5. A product according to claim 1 further comprising a carbohydrate source and a lipid source.

6. A product according to claim 5 in which the protein source comprises about 15% to about 35% of the total calories, the carbohydrate source comprises about 35% to about 60% of the total calories, and a lipid source comprises from 20% to about 40% of the total calories.

7. A nutritional product for delivering glutamine to a human or animal, the product comprising a protein source which includes a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof, and a source of lysine.

8. The product of claim 7 in which the protein source has an amino acid profile which fulfils the recommendations of the FAO/WHO expert committee for the essential amino acid requirements for children > 2 years of age.

9. The use of a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof, in the preparation of an enterally

administrable, nutritional product for delivering glutamine to a person in need thereof.

10. The use of a cereal protein selected from oat protein, sorghum protein and millet protein, or mixtures thereof, in the preparation of an enterally administrable, nutritional product for providing glutamine to patients suffering from injured or diseased intestines or to maintain the physiological functions of the intestine.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23L1/305

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 03543 A (CLOVIS GRAIN PROCESSING) 21 March 1991 see page 5, line 1-19 see page 27, line 30-38 see claims 1,4,6,10-14,18,21,22 see claims 28-30	1-3,7-10
X	WO 94 21141 A (KANSAS STATE UNIVERSITY) 29 September 1994 see claims	1-4,7-10
A	DE 297 11 429 U (A.REICHENAUER-FEIL) 6 November 1997 see claims	1-10
A	EP 0 705 542 A (SANDOZ NUTRITION) 10 April 1996 see claims	1-10

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1998	10/11/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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